SUPPORT FOR AMENDMENT

Claim 22 as amended is supported, in particular, by page 1, lines 1-3; page 12, lines 7-9 and page 13, line 24 of the specification as filed for amended clause a); page 14, line 25 for amended clause d); and page 14, lines 36-37 for amended clause f) of the specification as filed.

REMARKS

Claims 22, 45 and 46 are canceled. Claims 47-50 are added.

Claims 22-50 are now active and under consideration.

Applicant wishes to express sincere gratitude for the helpful and courteous discussion conducted with her U.S. representative, Mr. William Beaumont, on April 18, 2008. Further to, and consistent with, the remarks made during that discussion, Applicant wishes to make the following further remarks.

Claims 22-24, 26, 27, 32, 34, 38, 39 and 41-44 stand rejected under 35 USC 102 (e) as being anticipated by U.S. 7,033,757, i.e., the '757 patent.

However, this reference fails to either disclose or suggest the claimed invention for several reasons.

First, the '757 patent is directed to a different problem than the claimed invention.

In particular, the '757 patent describes a mutation scanning array which allows the identification of base pair mismatches in multiple genes or multiple copies of the same gene from different individuals simultaneously (See the Abstract). An example of how this method works is described at column 16, line 40 to column 17, line 5 and is repeated below for emphasis:

1. DNA to be screened (e.g. cDNA from an individual's lymphocyhtes) is digested to smaller fragments 950-300 base pairs) as detailed herein.

2. The digested fragments are self-hybridized to generate mismatches at positions of SNPs and mutatins. Self hybridization can be carried out by heating (e.g., 2 minutes, 96° C), then colling 65° C for 1 hour. Alternatively, to avoid heating which may generate unwanted abasic sites, addition of formamide plus moderate heating (40-70° C) can be used to perform the self hybridization.

3. Preferably, treatment with hydroxylamine follows, to remove unwanted abasic sites.

4. Treatment with mismatch repair glycosylases (Mut Y and TDG, separately or together) follows to convert mismatches to aldehydes.

5. Treatment with AED, FARP, BARP follows to label, e.g., fluoresceinate the generated aldehydes (corresponding to SNPs/mutations).

6. The sample is denatured, and directly applied to a DNA array, for example, DNA chips or beads where hybridization takes place.

7. Extensive washing follows, to remove unhybridized DNA or unbound FARP.

8. The label, e.g., fluorescence, from all elements on the DNA chip is read via appropriate devices (e.g. a scanning laser). These elements that display fluorescence correspond to gene fragments containing SNPs and mutations.

Thus, the '757 method uses the repair of a mutation using a glycosylase enzyme to generate a reactive aldehyde at the site of a base pair mismatch which the glycosylase enzyme has identified and acted upon. The DNA is then treated with a labeling compound

such as AED, FARP or BARP which reacts with the aldehyde group and labels the site of the mutation. These labeled DNA molecules are then allowed to anneal with a DNA target such as a DNA chip which can be read using a suitable device and so allow the relevant gene(s) to be identified as containing mutations.

DNA glycosylases are a family of enzymes involved in DNA repair. Glycosylases generate an apurinic or apyrimidinic site (AP) by removing the nitrogen base from a nucleotide while leaving the sugar-phosphate backbone intact. These AP sites are recognized by AP endonuclease enzymes which complete the rest of the repair. In '757 AP endonuclease enzymes are not present and so the apurinic or apyrimidinic site is instead free to react with a label.

In contrast, the claimed method is directed to a system for systematically and quantitatively screening one or more biological samples for their DNA repair properties. Claim 22 has been amended so as to specify that each repair solution contains labeled nucleotide triphosphastes. Such labeled nucleotide triphosphates are not used or described in '757.

Second, the method of '757 would not function using the labeled nucleotide triphosphates of the present invention, as an essential feature of the method according to '757 is the creation of the active aldehyde group as a result of the apurinic or apyrimidinic reactions mediated by the glycosylase. This active aldehyde group allows the associated DNA molecule to be labeled and fixed (see example 1 and 3 or '757) by the means described in '757. Labeled DNA molecules can then be recovered or used to probe a library/DNA chip to allow further analysis of the identified DNA mismatches. The use of Labeled nucleotide triphospates of claim 22 is neither described nor suggested in '757.

Each of claims 23-50 is also patentable with respect to '757 as each is dependent upon claim 22.

Third, the method of claim 22 further has an unobvious step with respect to '757. This is because the method of claim 22 and that of '757 relate to very different technical problems. Namely, the claimed method relates to a method for quantitatively determining the DNA repair properties of at least one or more biological median, whereas the '757 patent relates to a method for identifying mutations in large quantities of DNA from one or several samples for one or several genes simultaneously by generating reactive aldehyde groups at the site of base pair mismatches and labeling these for further analysis.

Further, the different methods of the claimed invention and the '757 patent not only address two different technical problems, but each uses different chemical reactions. Specifically, the claimed invention uses incorporation of labeled nucleotide triphosphates into DNA molecules which are being repaired (or not) by one or more of the biological media which supplement the repair solution, whereas the '757 patent uses the formulation of a chemically reactive aldehyde group at the site of a DNA mismatch which is then labeled and fixed to a substrate.

As noted above, the method of '757 would not function using the labeled nucleotide triphosphates of the claimed invention because glycosylases do not incorporate new nucleotides into a DNA molecule being repaired, but instead chemically modify one of the mismatched base pairs so that in conjunction with other repair enzymes a new nucleotide base is generated which is no longer mismatched. It would not be possible to modify the method of '757 to be the same as that of present claim 22 because one skilled in the art could not make use of labeled nucleotide triphosphates when using glycosylase enzymes as in the '757 patent..

Further, there would have been no reason or motivation for one skilled in the art to have modified the method of '757, since that method affords new and efficient means of identifying small numbers of base pair mismatches in very large quantities of DNA using glycosylases. Therefore one skilled in the art, in considering the '757 patent, and in wishing to devise a method to test the DNA repair properties of one or more biological media, would have developed a method based upon the use of glycosylases to test the efficacy of these biological media. This would be a fundamentally different system from the one defined by claim 22. Specifically, one would no longer be analyzing the effects *per se* of the biological media upon DNA repair, but instead the effects of these media upon the performance of the selected glycosylase. Hence, the '757 patent actually teaches away from the present invention.

Finally, it is noted that the '757 patent uses DNA chips in some of its examples as the means to identify which gene sequences correspond to labeled DNA fragments and, hence, have mutations. A DNA chip is a collection of microscopic DNA spots, commonly representing single genes, arrayed on a solid surface by covalent attachment to a chemical matrix. The only reactions which occur on these DNA chips are hybridization reactions between the labeled DNA and the covalently attached nucleotides. Thus, the '757 patent neither discloses nor suggests an array containing divided zones suitable for assessing different solutions as in the claimed invention.

Specifically, the '757 DNA chips are fundamentally different from the arrays, of the present invention, schematically depicted in FIG. 1 and FIG. 2 of the present specification, which each containing several zones, each zone having a deposit of the various plasmids and wherein each zone is exposed to a particular repair solution and then analyzed.

Therefore the array described in step c) of claim 22 has no equivalent in '757 and none of the structures described in '757 comprise the necessary features to act as the array which is described in step c).

Clearly, one skilled in the art would have had neither reason nor motivation from the '757 patent to have attained the claimed invention at the time it was made.

However, even assuming, *arguendo*, that the present invention would have been obvious, the present specification, itself, rebuts any presumption of obviousness.

First the claimed invention makes it possible to detect an overall effect, while identifying the various lesions, due to the possibility of simultaneously assessing the repair of various types of lesions.

Second, the claimed invention makes it possible to determine the excision and/or excision/resynthesis capacities of a biological extract without requiring a comparison with a control biological medium. This is because the results obtained by carrying out the claimed method with a single sample of biological extract is sufficient to afford the extract a repair effectiveness with respect to precise and quantified lesions.

Third, the claimed invention is particularly suitable for studying various biological media and is a good reflection of the situation *in vivo*.

Fourth, the claimed method makes it possible to "map" a given biological medium in terms of its enzyme activities for DNA repair. Further it is possible to identify a biological extract according to the map obtained.

Fifth, the claimed invention makes it possible to determine the repair proteins that are deficient or partially deficient in a given biological extract and, thus, serve as a diagnostic test.

Sixth, the claimed invention also makes it possible to compare the performance levels of various biological extracts in terms of DNA lesion repair.

Seventh, since the claimed invention can be practiced in miniaturization, it's possible to obtain numerous pieces of information using only very small amounts of biological material.

Finally, the claimed invention can be automated.

Here, for all of the above reasons, this ground of rejection is believed to be unsustainable and should be withdrawn.

Claims 22-46 stand rejected under 35 USC 112, second paragraph.

Notably, claim 22 has been amended to read --excision and resynthesis-- instead of "overall and specific".

Hence, in view of the above amendments and remarks, it is believed that this ground of rejection is moot.

Claims 45 and 46 stand rejected under 35 USC 112, first paragraph.

However, in view of the above amendments, it is believed that this ground of rejection is moot.

The Abstract has been objected to.

In view of the new Abstract submitted herewith, it is deemed that this objection is moot.

Consistent therewith, and with amended claim 22, a new Title is also hereby provided. Accordingly in view of all of the above, it is urged that this application is now in condition for allowance.

Further, claim 22, step d) has been amended to specify that each repair solution contains a labeled nucleotide triphosphate. Claim 22, step f) has been amended to accord with step d).

Accordingly, in view of all of the above, it is believed that the application is now in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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